PATENT
0259-0411P

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant:	DALLE CARBONARE, M. et al.	Conf.:	6340
Appl. No.:	10/019,387	Group:	1615
Filed:	March 26, 2002	Examiner:	Maewall, S.
For:	USE OF HYALURONIC ACID DERIVATIVES FOR THE PREPARATION OF PHARMACEUTICAL COMPOSITIONS AND BIOMATERIALS FOR THE PREVENTION OF THE FORMATION AND CURE OF CUTANEOUS SCARS		

DECLARATION SUBMITTED UNDER 37 C.F.R. § 1.132

Honorable Commissioner
Of Patents and Trademarks
P.O. Box 1450
Alexandria, VA 22313-1450

April 14, 2008

Sir:

I, Dr. Anna Maria Zanellato of the Fidia Farmaceutici, Italy, do hereby declare the following:

I have attached a copy of my curriculum vitae to this Declaration.

I am working as Scientific Assistant to the Patent Department and I have worked in the field of cellular biology for 13 years.

I am familiar with the above referenced patent application, as well as the development, usages and properties of hyaluronic acid derivates and their uses, in particular to reduce normotrophic scarring.

I have read and understand the subject matter of the Office Action of December 12, 2007.

The following comments are offered in support of the patentability of the instant invention.

The Examiner states that the instant invention is obvious over WO 99/04828 ('828) in view of WO 94/17837 ('837) and further in view of the Davidson et al. reference (Clinical Materials, 1991) and Ruiz-Cardona et al. (Biomaterials, 1996). In brief the Examiner states that '828 teaches that particular hyaluronic acid derivates can be used to treat adhesion and scar formation, '837 teaches a surface layer of at least one derivative of hyaluronic acid that comes in contact with the skin, Davidson et al. teaches hyaluronate derivates and their application to wound healing and wound repair with reduced scarring and that Ruiz-Cardona et al. teache application of benzyl hyaluronate as wound dressings. The Examiner concludes that a skilled artisan would have been motivated to use derivatives of hyaluronic acid such as esters of hyaluronic acid in treating scarring of the skin and treatment of a wound with a reasonable expectation of success. I disagree.

First, the '837 reference is directed to skin pathologies. Normotrophic scarring is not a skin pathology and '837 does not discuss normotrophic scarring at all. In addition, '837 states that hyaluronic acid derivates and/or their mixtures have (1) poor mechanical characteristics when wet due to its tendency to form a gel when in contact with aqueous fluids such as physiological fluids, (2) high cost and (3) excessively high vapour transmission values. The reference also states "[t]hese drawbacks are particularly significant in cases where poor exudate production is present" (emphasis added). Normotrophic scarring process does not depend on or produce exudate; that is

there is poor exudate production. Thus, the skilled artisan reading the '837 reference would not conclude that using hyaluronic acid to treat normotrophic scarring would be likely to succeed.

Second, Davidson et al. state on page 174, column 1, lines 3-8 and beginning at the last line on page 174, column 1 and ending at column 2, line 3 that the two hyaluronic acid formulations were not significantly different from control values. They also state on page 174, column 1 at lines 25-28 that none of the results for progression of wound healing parameters was statistically significant. Consequently, based on the disclosure of this reference, the skilled artisan would not have any expectation of success in using the claimed hyaluronic acid derivatives for reducing the amount of normotrophic scarring.

Third, Ruiz-Cardona et al. are only concerned with determining the CO_2, O_2 and water vapour transmission rates of membranes composed of benzyl hyaluronate esters to assess whether these membranes have potential as wound dressings. The reference makes no reference to the process of normotrophic scarring and, indeed, there are many wound dressings available which have no reducing affect on normotrophic scarring. Again, based on this disclosure the skilled artisan would have no expectation of success in reducing normotrophic scarring based on the teachings of this reference.

It seems that the Examiner has focused on the fact that hyaluronic acid has been suggested to be a good biomaterial for wounds and has ignored the fact that the claims are directed to the property of hyaluronic acid derivatives to reduce normotrophic scarring. This is the first report of the use of these compositions to accomplish that. Furthermore, it is not a property that is possessed by hyaluronic acid or its salts.

Example 1 in the Specification on page 27, beginning at line 24, presents the details of an animal study comparing the scarring resulting from treatment of a wound with partial ester of hyaluronic acid HYAFF ® 11p75 or hyaluronic acid. The results are presented in Figure 1, where it is clear that the improvement resulting from treatment with HYAFF is statistically signicantly better than from treatment with hyaluronic acid alone. This result could not have been predicted or expected from any of the prior art taken singly or together.

I have also attached the results of another study conducted, this time using the auto-crosslinked ester of hyaluronic acid. As can be seen from the results, it is possible to observe that the scarred areas of the group treated with the auto-crosslinked ester of hyaluronic acid are 50% less extensive than the control areas.

It is therefore my view that the Specification teaches an unexpected result that is not expected from the prior art and, in fact, is not even suggested by the prior art. If anything, the references cited, taken together in their entirety, would discourage the skilled artisan. The results of Example 1 and the results of the new study attached show that unlike the prediction of the prior art and the expectations that it teaches, the claimed invention does indeed reduce normotrophic scarring.

The undersigned hereby declares that all statements made herein based upon knowledge are true, and that all statements made based upon information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

DATED: April 14 2008

Dr. Anna Maria Zanellato

CURRICULUM VITAE
Anna Zanellato

I, Anna Zanellato, being duly sworn, depose and say that:

- I am an Italian citizen residing at Bovolenta, Padua, Italy
- I am familiar with the English language.

I further declare that:

- I graduated in Biology at the University of Padua in the academic year 1987
- I am author of 19 scientific publications.

Previous job experience:

- From 1987 to 1990 I worked at the University Department of General Pathology as researcher, where I was involved in a study pertaining to smooth muscles cell cultures; moreover I studied the variations in myosin compositions that occur in situations of vascular pathologies such as Hypertension and Atherosclerosis.

- In the years 1990-2001, I worked at Fidia farmaceutici as senior researcher and my research activity involved: analysis of the action mechanism of various trophic factors of the central nervous system; studies utilising neuronal cultures to select new, pharmacologically active, chemical molecules to prevent different types of neuronal pathologies; other studies concerning the growth and proliferation of bovine, rabbit, human, mesenchymal/articular/fibroblastic cell cultures on biomaterials.

Current job:

- I am working as Scientific Assistant to the Fidia farmaceutici. Patent Department, Italy.

Decrease in the area of cutaneous scarring in a rat model following treatment of the wound with the auto-crosslinked ester of hyaluronic acid and hyaluronic acid

The animals were sedated by intramuscular injection of ketamine/xilazine (0.1 mg/g). The backs of the animals were shaved, washed and disinfected with chlorhexidine and iodate solution.
Four full-thickness wounds were performed on each animal using a punch with a 6 mm diameter.

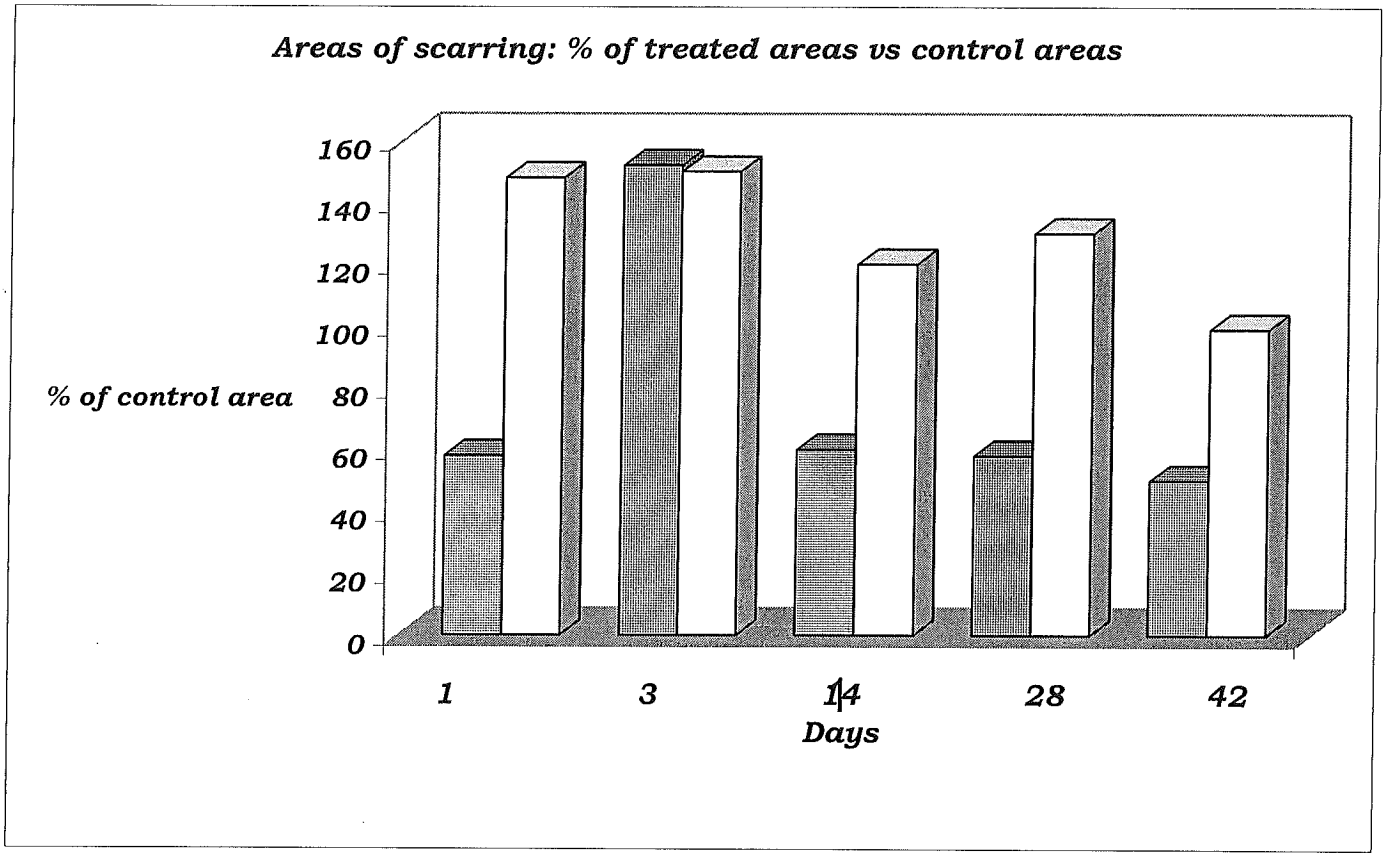
Treatment of wounds:

Groups	Number of treated sites	Treatment
1	18	Auto-crosslinked ester of hyaluronic acid in the form of gel, 30 mg/ml
2	18	Hyaluronic acid, Hyalastine® fraction, 60mg/ml

Hyaluronic acid Hyalastine® fraction (EP 138572)
Auto-crosslinked ester of hyaluronic acid (EP 341745) with a degree of 5% of the carboxyl groups crosslinked.

Two of the wounds in each animal were treated and two were used as control.
3 treated areas for group were removed at set times (1, 3, 7, 14, 28, 42 days). The samples were cut into sections and stained with Mallory's triple stain; the sections were analysed by optical microscope and the scarred areas was measured.
The graph reports values expressed as percentages of scar area of the treated sites compared to that of the untreated sites, and each value corresponds to the mean of three determinations on three different animals.

It is evident that a single application of the auto-crosslinked ester of hyaluronic acid is able to prevent the formation of scarring better than a single application of hyaluronic acid.
Indeed, as early as the 14th day, it is possible to observe that the scarred areas of the group treated with an auto-crosslinked ester of hyaluronic acid are 50 % less extensive than the control areas.



Columns on the left = ***autocrosslinked ester of hyaluronic acid***
Columns on the right = ***hyaluronic acid***